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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/719,867 | 12/28/2000 | Steven Alan Dunham | 5934-01-EMA | 5272 |

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| EXAMINER |
|---|
| TAYLOR, JANELL E |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | 10 |

DATE MAILED: 08/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/719,867 | Dunham | |
| | Examiner | Art Unit | |
| | Taylor, Janell | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election with traverse of groups II and III in Paper No. 9 is acknowledged. The traversal is on the ground(s) that all the strains and proteins of group II involve mutations in GyrA protein which confers antibiotic resistance, and likewise group III involve mutations in the FabI protein which confers antibiotic resistance and therefore they share a special technical feature. However, antibiotic resistance itself is not considered a "special technical feature". Although the groups are both drawn to genes which confer antibiotic resistance, they differ in both structure and function from each other, and therefore do not share a special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

### *Claim Rejections - 35 USC § 112*

2. Claims 1, 4-24, and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for identifying and characterizing mutations related to the quinolone resistance determining region of gyrA, wherein the entire gene is mutated, does not reasonably provide enablement for a process for identifying and characterizing mutations leading to a selectable phenotype comprising generating a defined set of overlapping 10kb products containing random point mutations which encompass the complete chromosome of any organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In Ex parte Forman, 230 USPQ 546 (Bd. App. 1986), the Board considered the issue of enablement in molecular biology. In considering these factors: (a) in order to practice the invention, the practitioner must be able to randomly mutate a complete chromosome of any organism, transform a host, isolate strains resistant to any compound, retransform sensitive bacteria with 10kb products, generate smaller PCR products, and sequence DNA from regions conferring resistance to identify the chromosomal mutation; (b) the specification provides guidance only for in the gyrA quinolone resistance determining region; (c) working examples are presented only for generation of N. gonorrhoeae strains with altered gyrA and parC alleles and identification of mutations responsible for ciproflaxicin resistance, and random mutations in the fabI gene; (d) the invention, as claimed, is directed to a process for identifying and characterizing mutations leading to a selectable phenotype of any gene in any organism; (e) the prior art teaches correlation of alterations in the GyrA subunit of DNA Gyrase and the ParC subunit of topoisomerase IV with antimicrobial susceptibility; (f) the level of skill in molecular biology is high; (g) the results of experiments involving any organism randomly mutated and transformed, wherein a mutation confers bacteria resistant to any compound, is not predictable; (h) the claims are broadly drawn, reciting any possible mutation in any organism leading to bacteria resistant to any compound. Based on the above analysis, one of ordinary skill in the art would be subject to undue experimentation in practicing the invention as claimed.

3. Claims 2 and 16-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, claim 2 states that certain mutations associated with quinolone resistance are detected, and are used to "help to understand the mechanism of action of quinolones, and other type IV topoisomerase inhibitors." There is not appropriate written description of how identifying those given mutations will forward the understanding of how quinolones, or other type IV topoisomerases, function.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 4, 8, and 16-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the phrase "12 PCR products corresponding to 100 kb of the chromosome into a wild-type background." This is confusing for several reasons. First of all, it is not clear if each of the 12 PCR products are 100kb each, or that is the sum total of all 12 products together. Secondly, it is unclear what a "wild type background" means. This is confusing because it is not clear if the organism which is transformed is the same as that of the organism of the first step, but is a wild type organism, or if the transformed organism may be a different organism. Thirdly, it is not clear what is meant by the term "background". This is a vague and confusing term, which does not completely describe what is meant. Appropriate correction and clarification of the claim is required.

6. Claim 1 recites the limitation "compound" in step c). There is insufficient antecedent basis for this limitation in the claim.

7. Claims 2 and 16-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Step "e" of claim 2 states that "new mutations associated with quinolone resistance", as listed, are identified. However, this is a confusing step because step "a" recites that the QRDR was mutagenized randomly. So it is unclear how certain "new mutations" may be said to have arisen when the gene was randomly mutated. Appropriate correction is required.

8. Claims 2 and 16-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2 recites the phrase "wild type background." This is a vague and confusing term, which does not completely describe what is meant. Appropriate correction and clarification of the claim is required.

9. Claims 6, 9, 15, and 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 recites the phrase "generating DNA fragments by PCR amplification of the bacterial chromosome corresponding to regions of the bacterial chromosome which may contain a mutation". It is not clear how only those regions of the bacterial chromosome which may cause a mutation are fragmented. Because the wording of the claim is ambiguous, it is unclear if the entire

chromosome is fragmented, or only those genes which may contain a mutation are fragmented. Appropriate correction is required.

10. Claims 16-21 recites the limitation "the antibacterial compound". There is insufficient antecedent basis for this limitation in the claim or in the claims from which they depend. Appropriate correction is required.

***Claim Rejections - 35 USC § 103***

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 5, 7,10-11 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kok et al. (Journal of Bacteriology, July 1997, pages 4270-4276, Vol. 179, No. 13) in view of Belland et al. (Molecular Microbiology, 1994, Vol. 14, No. 2, pages 371-382).

Kok teaches a method to identify mutations in a gene altering the natural function of a protein encoded by said gene. The pobA and pobR region of Acinetobacter strains were amplified with a Taq polymerase (page 4271, col. 1, lines 43-52). The bacteria were transformed and the resulting PCR products and viability were assessed by growth on selective media containing 4-hydroxybenzoate (page 4271, col. 1, lines 12-18 and 30-42). Mutations were mapped and the sequences analyzed (page 4271, col. 1, line 52 and col. 2, line 8). Mutations in the PCR products resulted in a selectable phenotype (page 4272, col. 1, lines 11-15). It was noted that analysis of a wide range

of chromosomal point mutations should be applicable to other genes in natural transformation systems and to study the structure-function relationship of proteins (page 4276, col. 1, lines 8-14).

Kok does not teach that an antibacterial compound is used for selection of transformed bacteria, or that the compound is an inhibitor of type II topoisomerases, or FabI, or in inhibitor or enzymes involved in fatty acid biosynthesis, or that the antibiotic compound is a fluoroquinolone, or ciprofloxacin.

Belland teaches that the antibacterial compound used for selection of transformed bacteria is the fluoroquinolone ciprofloxacin. Specifically, Belland teaches that the cipro is an inhibitor of type II topoisomerases.

It would have been obvious to combine Kok and Belland, as cipro is a well known antibiotic, and research on it would have been useful in determining which bacteria are likely to form a resistance to it, and what mutations cause a resistance to it.

13. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kok in view of Belland as applied to claim 5 above, and further in view of Pruna (USPN 5,532,239).

As disclosed above, Kok teaches a method to identify mutations in a gene altering the natural function of a protein encoded by said gene. The pobA and pobR region of Acinetobacter strains were amplified with a Taq polymerase (page 4271, col. 1, lines 43-52). The bacteria were transformed and the resulting PCR products and viability were assessed by growth on selective media containing 4-hydroxybenzoate (page 4271, col. 1, lines 12-18 and 30-42). Mutations were mapped and the sequences

analyzed (page 4271, col. 1, line 52 and col. 2, line 8). Mutations in the PCR products resulted in a selectable phenotype (page 4272, col. 1, lines 11-15). It was noted that analysis of a wide range of chromosomal point mutations should be applicable to other genes in natural transformation systems and to study the structure-function relationship of proteins (page 4276, col. 1, lines 8-14).

Kok does not teach that an antibacterial compound is used for selection of transformed bacteria, or that the compound is an inhibitor of type II topoisomerases, or FabI, or in inhibitor or enzymes involved in fatty acid biosynthesis, or that the antibiotic compound is a fluoroquinolone, or ciprofloxacin.

Belland teaches that the antibacterial compound used for selection of transformed bacteria is the fluoroquinolone ciprofloxacin. Specifically, Belland teaches that the cipro is an inhibitor of type II topoisomerases.

It would have been obvious to combine Kok and Belland, as cipro is a well known antibiotic, and research on it would have been useful in determining which bacteria are likely to form a resistance to it, and what mutations cause a resistance to it.

Neither Kok nor Belland teaches that the antibiotic is clinafloxacin.

Pruna teaches that clinafloxacin is a well known antibiotic (col. 2, lines 33-40).

It would have been obvious to combine Kok and Belland and Pruna, as clinafloxacin is a well known antibiotic, and research on it would have been useful in determining which bacteria are likely to form a resistance to it, and what mutations cause a resistance to it.

14. Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kok in view of Belland as applied to claims above, and further in view of Ibraham (USPN 5,145,667).

As disclosed above, Kok teaches a method to identify mutations in a gene altering the natural function of a protein encoded by said gene. The pobA and pobR region of Acinetobacter strains were amplified with a Taq polymerase (page 4271, col. 1, lines 43-52). The bacteria were transformed and the resulting PCR products and viability were assessed by growth on selective media containing 4-hydroxybenzoate (page 4271, col. 1, lines 12-18 and 30-42). Mutations were mapped and the sequences analyzed (page 4271, col. 1, line 52 and col. 2, line 8). Mutations in the PCR products resulted in a selectable phenotype (page 4272, col. 1, lines 11-15). It was noted that analysis of a wide range of chromosomal point mutations should be applicable to other genes in natural transformation systems and to study the structure-function relationship of proteins (page 4276, col. 1, lines 8-14).

Kok does not teach that an antibacterial compound is used for selection of transformed bacteria, or that the compound is an inhibitor of type II topoisomerases, or FabI, or in inhibitor or enzymes involved in fatty acid biosynthesis, or that the antibiotic compound is a fluoroquinolone, or ciprofloxacin.

Belland teaches that the antibacterial compound used for selection of transformed bacteria is the fluoroquinolone ciprofloxacin. Specifically, Belland teaches that the cipro is an inhibitor of type II topoisomerases.

It would have been obvious to combine Kok and Belland, as cipro is a well known antibiotic, and research on it would have been useful in determining which bacteria are likely to form a resistance to it, and what mutations cause a resistance to it.

Neither Kok nor Belland teaches that the antibiotic is triclosan or DHDPE.

Ibraham teaches both triclosan and DHDPE (Col. 2, lines 50-60).

It would have been obvious to combine Kok and Belland and Ibraham, as triclosan and DHDPE are well known antibiotics, and research on them would have been useful in determining which bacteria are likely to form a resistance to it, and what mutations cause a resistance to it.

15. Claims 6, 9, and 15, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Belland et al. in view of Jones et al. (Biotechniques, Vol. 10, No. 1, 1991, pages 62-66).

Belland discloses the identification of mutations within the gyrA gene. The gyrA region of ciproflaxin-resistant N. gonorrhoeae strains was amplified using PCR and mutations in the 'quinolone resistance-determining region' (amino acids 55-110, i.e. 168 nucleotides) at positions S91 and D95 were identified (page 376, table 3, and column 1, line 9, column 2, line 33). Cipro-resistant mutations were transferred back to the parental strain using whole cell DNA together with the natural competence of N. gonorrhoeae for DNA transformation, and transformants were again selected by their resistance to the antibiotic (page 376, col. 2, line 36, page 377, col. 1, line 8).

Belland does not teach DNA fragments are derived from PCR products.

Jones et al describes a PCR-based method that permits the generation of recombinant DNA products with homologous ends that undergo recombination following transformation with E. coli strains (page 62, Abstract, lines 1-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to used PCR fragments for transformation and homologous recombination in the transformation of N. gonorrhoeae. This would have allowed for smaller, more controlled fragments whose exact lengths and sequences would have been known, and the transformation would have been easier and more complete using PCR products than whole cell fragments.

16. Claims 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Belland et al. in view of Jones et al. and further in view of Wohlstadter et al. (USPN 6,087,177).

Belland discloses the identification of mutations within the gyrA gene. The gyrA region of ciproflaxin-resistant N. gonorrhoeae strains was amplified using PCR and mutations in the 'quinolone resistance-determining region' (amino acids 55-110, i.e. 168 nucleotides) at positions S91 and D95 were identified (page 376, table 3, and column 1, line 9, column 2, line 33). Cipro-resistant mutations were transferred back to the parental strain using whole cell DNA together with the natural competence of N. gonorrhoeae for DNA transformation, and transformants were again selected by their resistance to the antibiotic (page 376, col. 2, line 36, page 377, col. 1, line 8).

Belland does not teach DNA fragments are derived from PCR products.

Jones et al describes a PCR-based method that permits the generation of recombinant DNA products with homologous ends that undergo recombination following transformation with E. coli strains (page 62, Abstract, lines 1-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to used PCR fragments for transformation and homologous recombination in the transformation of N. gonorrhoeae. This would have allowed for smaller, more controlled fragments whose exact lengths and sequences would have been known, and the transformation would have been easier and more complete using PCR products than whole cell fragments.

Neither Belland nor Jones teach that the mutation is caused by a chemical mutagen or UV light.

Wohlstadter teaches different methods of mutation exist and may be used in conjunction one with another. Wohlstadter teaches both UV irradiation and chemical mutagens.

It would have been obvious to use the art of Wohlstadter with that of Belland and Jones, because UV irradiation and chemical mutation were both well known forms of causing mutations in the art, and would have allowed for random mutagenesis to occur at a controlled rate.

***Summary***

Claims 1, 2, 4-24, and 36 are rejected under 35 U.S.C. 112, first paragraph. Claims 1, 2, 4, 6, 8, 9, and 15-24 are rejected under 35 U.S.C. 112, second paragraph. Claims 5-7,9-15, 22-24 and 36 are rejected under 35 U.S.C. 103(a). No claims are allowable.

***Conclusion***

Any inquiries of a general nature relating to this application, including information on IDS forms, status requests, sequence listings, etc. should be directed to the Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janell Taylor Cleveland, whose telephone number is (703) 305-0273.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (703) 308-1152.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1634 via the PTO Fax Center using (703) 872-9306 or 872-9307 (after final). The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Janell Taylor Cleveland

July 30, 2002

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Supervisory Patent Examiner
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